INTRODUCTION

Topical therapeutics to eyes is administered in form of eye drops, ointments, gels, ocuserts and soft contact lenses. Among all topical delivery systems, eye drops are effortless and most convenient mode of administration. Eye drops are further classified as solutions and suspensions constituting more than 90% of currently accessible marketed ophthalmic formulations. These conventional dosage forms have poor bioavailability due to precorneal loss, transconjunctival systemic absorption and drainage. Various anatomical barriers such as corneal epithelium (hydro-lipophilic nature) impede transport of both hydrophilic and lipophilic drugs. Also, eye drops have major limitations of quick dilution and washing out. Due to these limitations only 5% of administered drug reaches the aqueous humor and most of the drugs are eliminated without absorption.

Eye ointments increases bioavailability of drug by increasing contact time however these formulations have drawbacks of blurring of vision and delayed onset of action. Gels provide longer contact time (compared to ointments) with no blurring of vision but manufacturing cost of the formulations is relatively very high. Ocuserts are used for prolonged delivery of drugs with constant rate through membrane with minimal side effects; whereas, soft contact lenses deliver high concentration of antiviral, antibiotics and anti-glaucoma drugs. However patient compliance is major limitations for ocuserts and soft contact lenses.

Ocular parameter influencing topical bioavailability

Eye is separated from rest of the systemic access by blood retinal, blood-aqueous and blood-vitreous barriers making topical therapy most suitable for ocular manifestations. The highly specialized ocular barriers control the inward and flow of compounds.

Precorneal parameters

Less capacity of cul-de-sac

Eye drops are instilled in cul-de-sac. Cul-de-sac has a maximum capacity of 30 µl in humans. When the lower eyelid returns to its normal position the capacity of the conjunctival sac shrinks by 70% to 80% to less than 10 µl. Further the capacity of cul-de-sac can be reduce by various pathological conditions such as cicatricial, allergic or inflammatory process and disabled patient. Moreover the capacity of cul-de-sac is reduced by blinking.

Elimination of drug from lachrymal fluid

At precorneal site drugs are mainly eliminated by solution drainage, lachrymation and nonproductive absorption to the conjunctiva. Conjunctiva is thin membranous vascularised part that absorbs most of the topically applied drugs. For few drugs such as β-blockers conjunctival permeability coefficients are greater the corneal permeability coefficient causing absorption of drugs to systemic circulation.

At the time of application almost 30 µl of volume is instilled to eyes but instilled dose is rapidly removed from lachrymal drainage or through lachrymal drainage system until tear return to its normal volume i.e. 7µl. Tear turnover also plays a minor role in clearance of drug leading to lesser corneal absorption. Also drug metabolism and drug protein binding into tears hinders absorption to an extent.

Received: 23-03-2018; Revised: 18-04-2018; Accepted: 03-05-2018.

Keywords: Nanoemulsion, Ophthalmic, Sustained Drug Delivery, Micelles.
**Corneal parameter**

Cornea provides major barriers for penetration of drugs into deeper tissues. Cornea functions as a trilaminar permeability barrier. The epithelium and endothelium being hydrophobic in nature are main barriers to hydrophilic molecules. Tight Junctions that are formed by apical corneal epithelial cells, limit drug absorption from the lachrymal fluid into the eye. The stroma is hydrophilic in nature. Hence these barriers provide major resistance for both hydrophilic and hydrophobic molecules\(^{15}\).

**Blood-ocular barriers**

The blood-ocular barriers prevent access of hydrophilic drugs in aqueous humor. Retinal pigment epithelium (RPE) and tight walls of retinal capillaries form posterior barrier. This is a barrier between blood stream and eye. Distribution of drugs into retina is limited by the RPE and retinal endothelia\(^{15}\).

**Various delivery systems for improving topical bioavailability**

Various ocular therapeutic systems have been tried to improve the ocular bioavailability of both hydrophilic and lipophilic drugs. However these systems are associated with limitations that make these formulations intricate for manufacturing and commercialization (Table 1).

**Nanoemulsion system: a potential technique for ocular drug delivery**

Nanoemulsions are thermodynamically stable dispersed, micro-heterogeneous, multi-component, surfactant containing optically isotropic, transparent or translucent clear system\(^{61,62}\). Nanoemulsions are acceptable as water-continuous ophthalmological carrier systems due to their dilution with physiological water giving extraordinary continuous ophthalmological carrier systems due to their clear system containing optically isotropic, transparent or translucent.

Nanoemulsion formulations penetrate more into deeper layers of ocular tissues than the native drug.

Nanoemulsion is spread nicely on the cornea due to its low surface tension. It further improves mixing with the precorneal film constituents. Contact time between the drug and corneal epithelium is improved due to uniform spreading and mixing of nanoemulsion formulation in eyes. Also its micellar structure mimic tears, that further increases corneal adherence of the formulation.

**Exploring nanoemulsion for sustained topical ocular delivery**

In nanoemulsion system, drug gets partitioned between dispersed and continuous phases. Drug can be transported through the semi-permeable membrane if the nanoemulsion system comes in its contact. Drug releases from nanoemulsion system with pseudo-zero order kinetics. Drug release from nanoemulsion system also depends on volume of dispersed phase, partition coefficient and the transport rate of the drug.

Gallarate et al. (1993) prepared oil-in-water (O/W) nanoemulsion containing levobunolol. The study revealed a reservoir effect of drug in nanoemulsion showing prolonged drug release\(^{65}\). Naveh et al. (1994) developed a nanoemulsion formulation of pilocarpine using MCT, E-80 phospholipids, miranol MHT solution, \( \alpha \)-tocopherol and water. The nanoemulsion formulation showed a prolonged hypotensive action in normotensive rabbits after topical administration. The formulation was found to be of substantial importance as aqueous pilocarpine solution is administered 3 to 4 times a day for treatment of glaucoma. Moreover the multiple dosing causes side effects such as miosis leading to blurring of vision and also thought to be cataractogenic. The formulation showed a prolonged hypotensive effect for 11 hour post instillation and it was increased to 29 hour during follow up\(^{67}\). Mutchar et al. (1997) prepared submicron O/W emulsion of indomethacin using purified phospholipids mixture, \( \alpha \)-tocopherol, MCT and water. The ex vivo permeation studies indicated apparent corneal permeability coefficient of indomethacin incorporated in system is 3.8 times greater than that of marketed aqueous solution -Indocollyre\(^{68}\). The formulation shows purportedly better bioavailability and retention\(^{68}\).
Table 1: Various delivery systems for improving topical bioavailability and problem associated:

<table>
<thead>
<tr>
<th>S. No</th>
<th>Delivery system(s)</th>
<th>Advantage over conventional delivery system</th>
<th>Disadvantages</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| 1     | Ocular inserts     | • Increased ocular residence with controlled release  
                          • Reduction of systemic absorption  
                          • Reduced frequency of administration  
                          • Targeting of intraocular tissues through non-corneal route | • Difficulty in insertion  
                          • Irritation due to penetration enhancers | 16-18 |
| 2     | Nano-suspensions  | • Can be commercialized easily with long term physical stability  
                          • Very good technique for sparingly water soluble drugs  
                          • Extended release, improved bioavailability with no toxicity | • Abrasion of grinding ball leading to high metal content of formulation | 19-23 |
| 3     | Hydrogel systems  | • Controlled drug delivery using biodegradable polymers  
                          • Extended release | • Blurring of vision | 24,25 |
| 4     | Liposomes         | • Improved ocular bioavailability by interaction between liposome and cells through surface absorption, endocytosis, lipid exchange between walls and merging of membrane  
                          • Biodegradable, biocompatible and non-immunogenic. | • Very high manufacturing cost  
                          • Poor stability (phospholipids are prone to oxidative degradation).  
                          • Leakage and fusion of drugs | 26-33 |
| 5     | Niosomes          | • Improved ocular absorption  
                          • More stable, flexible and achieves better entrapment of hydrophilic drugs.  
                          • Increased ocular bioavailability of drugs; surfactants act as penetration enhancers as they can remove the mucous layer and break junctional complexes.  
                          • Biodegradable, biocompatible, least toxic and non-immunogenic. | • Aggregation, fusion, leaching, or hydrolysis of encapsulated drug, thus reducing shelf-life of niosomal preparation  
                          • May be irritant to eye. | 27,34,35 |
| 6     | Discomes          | • Better entrapment and bioavailability of hydrophilic drugs compared to niosomes. | • High manufacturing cost.  
                          • Discomes formulation can cause irritation to eyes. | 27,36 |
| 7     | Solid Lipid Nanoparticles (SLNs) | • High drug loading capacity for lipophilic and possibly hydrophilic drugs.  
                          • Suitable to sterilization by autoclaving.  
                          • Improved ocular bioavailability.  
                          • Prolong ocular retention time.  
                          • Sustained release. | • Drug expulsion after polymeric transition during storage  
                          • Hydrophilic drugs in SLN systems show burst effects. | 27,37-39 |
| 8     | Polymeric nanoparticles | • Improvement in ocular drug penetration with prolonged action  
                          • Use of biodegradable, biocompatible, nontoxic, non-immunogenic polymer  
                          • Nanocapsules more bio-available because of their bioadhesive properties. | • High production cost.  
                          • Aggregation, fusion, or leaching of encapsulated drug, thus reducing shelf-life of formulations | 40-42 |
| 9     | Microspheres      | • Controlled delivery of drugs  
                          • Mucoadhesive property of microsphere helps in improved bioavailability.  
                          • Reduced toxicity. | • Burst effect.  
                          • Difficult to manufacture and high p cost. | 43-45 |
| 10    | Lipid emulsions   | • Enhanced ocular penetration and bioavailability  
                          • Enhanced drug solubilization. | • Hydrophilic drugs cannot be incorporated into this system. | 46-47 |
| 11    | In-situ gelling system | • Prolong effect  
                          • Improved retention time. | • Blurred vision.  
                          • Sticking of eyelids. | 1,48-51 |
| 12    | Contact lenses    | • Rate of drug delivery can be controlled | • May affect iris, conjunctiva and cornea | 52-53 |
Table 2: Nanoemulsion for topical ocular delivery

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drug</th>
<th>Solubility In water at 25°C (mg/ml)</th>
<th>Surfactants and co-surfactants</th>
<th>Oil</th>
<th>Comment</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Levobunolol</td>
<td>0.251</td>
<td>Lecithin, glycerol</td>
<td>Soybean oil</td>
<td>Increased in vitro permeability with a reservoir effect</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>Timolol</td>
<td>2.74</td>
<td>Lecithin</td>
<td>Isopropyl myristate</td>
<td>Bioavailability of nanoemulsion in aqueous humour was 3.5 times greater than Timolol alone</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>Indomethacin</td>
<td>3.11×10⁻³</td>
<td>Phospholipids Miranol – MHT</td>
<td>MCT</td>
<td>Considerable increase in corneal permeability compared to Indocolyre® (marketed formulation) showing almost 4 times corneal permeability coefficient with no toxicity in ex vivo studies</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Dexamethasone</td>
<td>0.08</td>
<td>Cremophor EL, Propyleneglycol,</td>
<td>Isopropyl myristate</td>
<td>Improved ocular bioavailability( almost three times compared to conventional dosage form) and sustained effect of drug with no ocular irritation</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>Chloramphenicol</td>
<td>2.5</td>
<td>Span20, Span80, Tween20, Tween80</td>
<td>Isopropyl palmitate and isopropyl myristate</td>
<td>Improved stability in nanoemulsion of conventional system as chloramphenicol is quite susceptible to degradation in conventional dosage form</td>
<td>72,73</td>
</tr>
<tr>
<td>6</td>
<td>Pilocarpine</td>
<td>31.3</td>
<td>Macrogol 1500-glyceroltriricinoleate, PEG 200, propylene glycol,</td>
<td>Isopropylmyristate</td>
<td>Improved ocular bioavailability to upto 1.68 times with sustained effect compared to aqueous solution with no ocular toxicity</td>
<td>70</td>
</tr>
</tbody>
</table>
Fialho and da Silva-Cunha (2004) prepared a topical O/W nanoemulsion for topical ocular administration of dexamethasone. The results have shown the sustained release of drug hence reducing frequency of administration. Chan et al. (2007) formulated phase transition O/W nanoemulsion of pilocarpine. Sorbitan-mono-laurate and polyoxyethylene sorbitan-mono-oleate were used as non-ionic surfactant, ethyl-oleate as oil and water as aqueous component. All formulations showed a very good precorneal retention compared to pilocarpine in solution form. The miotic response was obtained after 130 min post administration of formulation. The nanoemulsion formulation showed a better hypotensive effect compared to pilocarpine solution. Various nanoemulsion formulations for ocular use are listed in Table 2.

Nanoemulsion formulations have shown its reservoir effect and sustained release behavior in various other routes showing a potential candidate for sustained release. Dalmora et al. (2001) reported sustain release of piroxicam from nanoemulsion of piroxicam. Kawakami et al. (2002) prepared nanoemulsion formulation of poorly water soluble drug (nitrendipine as model drug) and depicted sustained release of formulation in in vitro and in vivo studies. Mehta et al. (2007) formulated rifampicin O/W nanoemulsion containing oleic acid, phosphate buffer (PB), Tween 80 and ethanol for oral delivery. In vitro dissolution studies showed a sustained release profile of drug.

CONCLUSION

Eye diseases are the major cause of blindness in human. A WHO study has indicated approximately 161 million visual impairment cases worldwide, out of which 37 million were blind. Topical ocular delivery of drugs is pertinent for ocular manifestations and preferred over systemic route. Marketed ocular solutions and suspensions have considerable bioavailability issues with frequent dosing. Nanoemulsion is a thermodynamically stable and easily manufactured system that has huge potential in enhancing bioavailability and reducing frequency of administration.

Various surfactant, co-surfactant, oily and aqueous phases are approved by various regulatory agencies including USFDA for ocular instillation. Amount of surfactant used in nanoemulsion systems is major limitation as formation of nanoemulsion system requires high concentration of surfactants. Use of non-ionic surfactants can resolve the issue as they have minimum toxicity. Formulation evaluation parameters such as refractive index, pH, osmolality and viscosity nanoemulsion systems can easily be estimated.

Nanoemulsion systems have been explored for ocular use in previous few decades. The inherent property of sustaining the drug release makes it more patient complaint. Use of a nanoemulsion system for topical ocular therapeutics can overcome the limitation of multiple daily dosing with enhanced bioavailability. Moreover the nanoemulsion formulations are easier to formulate, scale up and do not require sophisticated instrumentation.

REFERENCES


